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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/721,864	11/24/2000	David Scheinberg	D6126	4077

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Dr. Benjamin Adler
McGREGOR & ADLER, LLP.
8011 Candle Lane
Houston, TX 77071

EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/721,864	SCHEINBERG ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date. _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 7 are being examined.

Withdrawn Rejection

The 103 rejection was withdrawn in view of the amendment, and replaced with a new 103 rejection.

New Rejections Based on The Amendment

Claim Rejections - 35 USC § 112 First Paragraph, New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 7 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention.

The limitation of "from about 20 mCi/mg to about 30 mCi/mg" claimed in Claims 1, 7 has no clear support in the specification and the claims as originally filed.

A review of the specification discloses support for a range from about 0.05 mCi/mg or 0.1 mCi/mg to about 100 mCi/mg (original claims 4, 13 respectively)

There is nothing in the specification to suggest or teach the specific range of "from about 20 mCi/mg to about 30 mCi/mg". The subject matter claimed in claims broadens the scope of the invention as originally disclosed in the specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1,7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simonson et al, 1990, Cancer Res, 50 (3 Supp): 9855-9885, of record, in view of Kasperson, FM et al, 1995, Nuclear Med Comm, 16: 468-476, of record, Vieira, MR, et al, 1996, Eur J Surgical Oncology, 22(4): 331-4, of record, and US 6,197,278, of record, and further in view of Kozak et al, 1986, PNAS, USA, 83(2): 474-8.

Claim 1 is drawn to: A method of increasing the probability of remission after treatment in an individual having a solid cancerous tumor greater than 1 mm in size, comprising the steps of:

(a) selecting an antibody that targets a specific binding site on a tumor cell comprising the solid tumor;

(b) selecting a high specific activity for a bismuth-213/antibody construct from about 20 mCi/mg to about 30 mCi/mg, said construct comprising bismuth-213 conjugated to said antibody via a bifunctional chelant;

(c) selecting a dose of said construct to provide a pharmacologically effective amount of antibody to saturate said targeted binding sites on an outer layer of tumor cells comprising the solid tumor so that more than two atoms of bismuth-213 delivers at least one alpha particle to each targeted tumor cell comprising said outer layer upon binding the antibody thereto;

(d) intravenously administering the dose of said high specific activity construct to said human, whereupon the tumor cells receiving said alpha particle are killed; and

(e) repeating step (d) wherein each repetition kills an additional layer of tumor cells thereby sequentially reducing the size of the solid tumor, thereby increasing the probability of remission in the individual.

Claim 7 is drawn to: The method of claim 1, wherein said dose is from about 0.1 mg/m^2 to about 10 mg/m^2.

Simonson et al teach i.p. administration of **212-Bi labeled antibodies** specific for the mucin antigen TAG-72 into mice previously injected with LS1744T cells. Simonson et al teach that LS1744T cells grow both as solid tumors and ascites in mice, wherein after the development of solid tumor, the mice develop ascites at about 20 days after injection of the tumor cells (p. 985s, second column, last paragraph, and p. 987s, second column, first paragraph). Simonson et al teach that the specific activity of the labeled antibody is 5 to 10 uCi/ug (p.986s, first column, second paragraph), which is the same as 5 to 10 mCi/mg. Simonson et al further teach that for advanced tumors of 13 days after injection of tumor cells, with single and repeated administration of Bi-212 labeled antibody, 56% decrease in tumor mass is obtained (p.986s, first column, third paragraph and figure 1 on page 986s). Simonson et al teach that 13 days after injection, the tumor mass is 3 gm on average (figure 1). Simonson et al teach that the efficacy of the treatment would be **even better** if the radiolabeled antibody recognizes an **antigen on cell surface** of target cell, rather than the mucin antigen TAG-72, which is secreted (p.987s, second column).

Simonson et al do not teach a method of killing a tumor greater than 1 mm in size, comprising intravenously administering antibodies that are labeled with Bi-213, having a specific activity from about 20 mCi/mg to about 30 mCi/mg and at a dose adequate to deliver a minimum of 1 alpha track per cell, or at a dose of about 0.1 mg/m^2 to about 10 mg/m^2.

Although Simonson et al do not teach that the treated tumors are at least 1 mm in size, one would have expected that the size of the solid tumors taught by Simonson et al would be at least **1 mm** in size, because the solid tumors taught by Simonson et al have 3gm average in weight, and are advanced tumors after 13 days of growth.

Kaspersen et al teach that **Bi-213** is an alternative to Bi-212, with the advantage of safer and easier production (p.475, first column, first paragraph).

Vieira, MR, et al teaches that imaging of breast cancer tissues could begin 10 minutes after **intravenous** administration of radiolabeled monoclonal antibodies (abstract, p.332, third paragraph). In other words, radiolabeled monoclonal antibodies could reach the breast cancer tissues within minutes after its intravenous administration.

US 6,197,278 teaches that after i.v. administration, localization of a radiolabeled targeting protein, annexin, a protein having high affinity for anionic phospholipid surface, in the target tissue can be obtained in only a few minutes (columns 9-10, especially last two paragraphs of column 9, bridging column 10).

Kozak et al teach use of bis-212 radiolabeled antibodies to **a cancer cell surface antigen**, interleukin-2 receptor, for killing T-cell leukemia while binding to the target cells (abstract, p.475-476). Kozak et al teach that the specific activity of the antibody is from 1 to 40

microCi/microgram (abstract), which is the same as **1-40 mCi/mg**, and is within the range of the claimed specific activity.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to **substitute Bi-212 with Bi-213** in the method of treating cancer taught by Simonson et al, because Bi-213 has the advantage of safer and easier production, as taught by Kasperson et al. It would have been obvious to replace antibodies specific for the mucin antigen TAG-72 taught by Simonson et al, with an antibody that targets a membrane cancer specific antigen on cancer cells, as suggested by Simonson et al, because an antibody to a cancer membrane antigen would be more effective than an antibody to a secreted antigen for targeting a cancer cell.

It would have been obvious to use a Bi-213 radiolabeled antibody with a specific activity higher than 10 mCi/mg taught by Simonson et al, such as the specific activity taught by Kozak et al, for optimization of the ranges of the specific activity of the antibody for immunotherapy. It is noted that to determine optimum concentration of reactants is within the level of ordinary skill in the art. See *In re Kronig*, 190 USPQ 425, and that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See also *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). With regards to the dosage of the labeled antibodies recited in claims 1, 7, to determine optimum dosage is within the level of ordinary skill in the art. See In r.ee Kronig, 190 USPQ 425.

It would have been obvious to administer the labeled antibody intravenously, because it is a convenient, alternative, routine route of administration of labeled antibodies for

immunotherapy. It would have been obvious to administer the labeled antibody once or repeatedly, as taught by Simonson et al, to ensure destruction of cancer cells.

One would have expected that the Bi-213 radiolabeled antibody would reach the target cancer cells within minutes after its intravenous administration, and that the Bi-213 radiolabeled antibody would have ample time to kill target cancer cells, despites the relative short half life of alpha particle, such as Bi-213, because targeting compounds, including radiolabeled antibody, have been shown to be able to reach the target cells within minutes after their intravenous administration, as taught by Vieira, MR, et al, and US 6,197,278.

One of ordinary skill in the art would have been motivated to treat tumors having at least 1mm in size using an antibody labeled with Bi-213, that targets a specific binding site on tumor cells, with a reasonable expectation of success.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
February 20, 2008

/Larry R. Helms/

Supervisory Patent Examiner, Art Unit 1643